Neratinib a MST 1 Inhibitor Coated With Chitosan-Alginate Nanocarrier As A Promising Oral Drug To Inhibit Pancreas Cell Apoptosis, Stimulate Insulin Secretion, And Restore Glycemia In Type 1 Diabetes

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NERATINIB A MST 1 INHIBITOR COATED WITH CHITOSAN-ALGINATE NANOCARRIER AS A PROMISING ORAL DRUG TO INHIBIT PANCREAS CELL APOPTOSIS, STIMULATE INSULIN SECRETION, AND RESTORE GLYCEMIA IN TYPE 1 DIABETES MELLITUS

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ABSTRACT

Type 1 Diabetes Mellitus (T1DM) is a polygenic disorder in which autoimmunity destroys pancreatic beta cells, culminating in an absolute insulin secretion deficiency. Neratinib is an MST1 inhibitor to improve β-cell survival cells coated with alginate calcium nanocarrier encapsulated with chitosan that allows the retention of the packaged oral drug until it reaches specific target cells. This review aims to determine the potential of Neratinib as a Mammalian sterile 20-like kinase 1 Inhibitor, which is carried by nanocarrier chitosan-alginate as an alternative cutting edge oral drug for T1DM by preventing the apoptosis of beta cells.. Neratinib coated with chitosan-alginate nanocarrier and packaged in the form of an oral drug can be used as an advanced T1DM therapy. Future perspective needs further experimental and clinical trials to obtain concrete scientific evidence.

Keywords: *Chitosan-Alginate Nanocarrier, MST1 inhibitor, Neratinib, Type 1 Diabetes Mellitus*

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INTRODUCTION

Diabetes mellitus is a metabolic disease characterized by chronic hyperglycemia because of defects in insulin secretion, insulin action, or both. Diabetes is classified into two types.Type 1 Diabetes Mellitus (T1DM) is a polygenic disorder in which autoimmunity destroys pancreatic beta cells, culminating in an absolute insulin secretion deficiency that does not recover.Type 2 Diabetes Mellitus (T2DM) is a type of diabetes induced by insulin resistance and inadequate insulin secretion response due to genetics and an unhealthy lifestyle, as well as inadequate glucose reabsorption in the kidneys [1-3].Almost 50% of T1DM patients will acquire a significant complication, such as losing eyesight, and developing end-stage renal disease.The disease is incurable, and the patient may develop neuropathy, vision loss, and coronary artery disease [4].

The prevalence of diabetes has continued to rise rapidly in low-middle income countries. Diabetes will affect 463 million people worldwide in 2019 and will reach 700 million by 2070. Diabetes is responsible for 11.3% of all fatalities among adults aged 20 to 79 worldwide. In 2012, there were 1.5 million deaths from diabetes Mellitus in the world. There were 3.7 million deaths associated with high blood glucose levels, with 43% in the under 70 age group. There was an increase in diabetes mellitus in 2019 to 4.2 million people [3, 5-6]. According to a meta-analysis review, the global incidence of type 1 diabetes was 15 per 100,000 persons in 2019, with a prevalence of 9.5%, particularly among children aged 14 [7-8]. There are 1–10 per 100 patient-years in children with established T1DM with ketoacidosis diabetic, and has 13–19% mortality rate [9].

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Currently, the management of T1DM can be divided into two methods, non-pharmacological and pharmacological. Non-pharmacological management is to identify people with risk factors, educate patients, manage obesity with medical nutrition therapy and physical exercise, and support healthier lifestyle changes [10]. The pharmacological management is insulin. However, the patient needs increased dose and the regimen complexity over time. Insulin therapy can increase the chance of severe hypoglycemia and the potential increased risk for hepatobiliary, colon, and breast cancer that can cause mortality [11]. A few drugs are used as T1DM therapy adjuvants, such as amylin analog, incretin-based agents, biguanides, Sodium-Glucose Cotransporter-2 (SGLT-2) inhibitor, and metformin. Rather than to improve glycemic control, their purpose is to control weight, give vascular endothelium protection, and protect the kidney's nephron [12]. Beta-cell replacement is usually applied for people with T1DM with complications. However, it is considered invasive. Islet transplantation is a less invasive surgical option for beta-cell replacement in patients with unstable diabetes. But it is still considered experimental in a few countries [13-14].

For decades, scientists have been working to make significant breakthroughs in diabetes mellitus treatment using biomolecular pathways. Mammalian sterile 20-like kinase 1 (MST1) is a significant regulator of pancreatic β cell death and dysfunction, lack of restoring functional β-cells, and normoglycemia. Identifying MST1 inhibitors, such as Neratinib, is a promising approach to the therapy of β cell-protective diabetes and can induce insulin secretion [15-16]. Nanoparticles have also been studied extensively over the last few decades. The nanoparticles allow the retention of the packaged drug until it reaches specific target cells. This specific targeted therapy is expected to reach the pancreas in terms of preserving its function efficiently. Among them is chitosan (CS) and alginate (ALG). Another water-soluble natural linear polysaccharide, ALG, is a popular pH-responsive polymer because it shrinks at lower pH, allowing encapsulated drugs to remain in the stomach while protecting against enzymatic deactivation [17].

Innovations can be done by modifying the delivery of neratinib using nanocarrier chitosan and alginate with oral administration to be more effective and protect the pancreatic cell from apoptosis. The purpose of this Literature Review is to find out the potential of neratinib, an MST1 inhibitor, channeled using Chitosan-Alginate Nanocarrier orally as a treatment of Type 1 Diabetes Mellitus

REVIEW

Pathophysiology of Type 1 Diabetes Mellitus in Hippo Pathway

The Hippo pathway was first found in Drosophila melanogaster twenty years ago, and it has recently been studied in mammals. *MST1* kinase acts as an essential regulator in adhesion, migration, growth, apoptosis, and T cell selection. The functional outputs of MST1 in mammalian cells are not limited to YAP/TAZ (Yes-associated Protein/Transcriptional Coactivator With PDZ-binding Motif) [18-19]

Hippo pathways on the pancreatic islet regulate the survival of beta cells and insulin secretion. Upstream signals, such as cell polarity, cell interaction, cellular stress, dynamic mechanical force of actin cytoskeleton, connective tissue growth factor (CTGF) signalling, and others, regulate Hippo Pathway [20]. This time, we will focus on discussing the MST1/2 pathway inhibited by neratinib.

Hippo Pathway is affecting apoptosis of beta-cells pancreas (Figure 1). Proteins control its regulation, for instance, merlin, MST1, and YAP. As a protective signal against apoptosis, YAP provides intrinsic resistance in beta cells. MST1 is an essential apoptosis molecule activated by oxidative stress, glucotoxicity, proinflammatory cytokines, and high levels of

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free fatty acids [20-21]. When MST1 is activated through JNK (Jun N- terminal Kinase), it stimulates BIM (a mitochondrial pro-apoptosis protein) to block BCLxL and BCL-2 (anti-apoptosis proteins). This caused BAX (BCL2 Associated X) to produce mitochondrial cytochrome C, which binds to APAF1 (Apoptotic protease activating factor 1). Both proteins will activate the apoptosome to remove Caspase9 and split into Caspase3. Casp3 will cut MST1 into fragments that can cause apoptosis. Casp3 can also directly cause beta-cell apoptosis, eventually leading to diabetes mellitus [16].

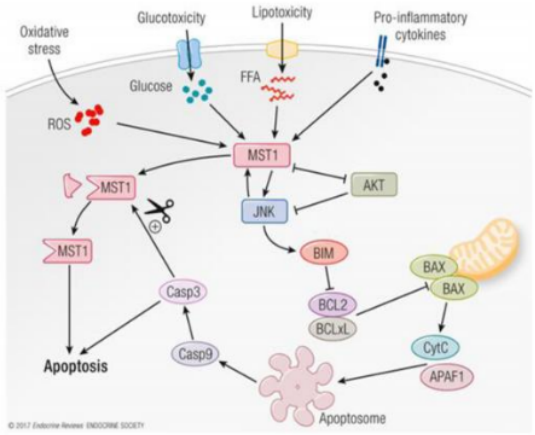

Figure 1. Hippo Pathway in Beta-cell Apoptosis [16]

Besides that, Hippo Pathway influences insulin secretion through PDX1 (pancreatic and duodenal homeobox 1) (Figure 2) by determining cell specification, beta-cell survival, insulin expression, and controlling genes to identify glucose and insulin secretion [20,22]. In unstressed beta-cell, PDX1 located in the nucleus and regulates gene expression to identify glucose and insulin secretion i.e. SLC2A2 (for GLUT2), GCK (glucokinase), and ins (insulin). Because of glucolipotoxicity and cytokine proinflammatory, stressed beta cells make MST1 and its fragments cut by Casp3 translocated to the nucleus and phosphorylated PDX1 directly. Phosphorylated PDX1 translocates into the cytoplasm and gets degraded, which causes the target cannot to express itself. It results in an abnormality of insulin secretion that will eventually cause diabetes mellitus if the body fails to compensate over time [16].

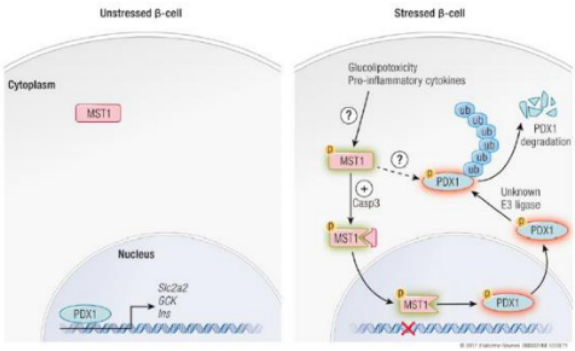

Figure 2. Hippo Pathway in Insulin Secretion [16]

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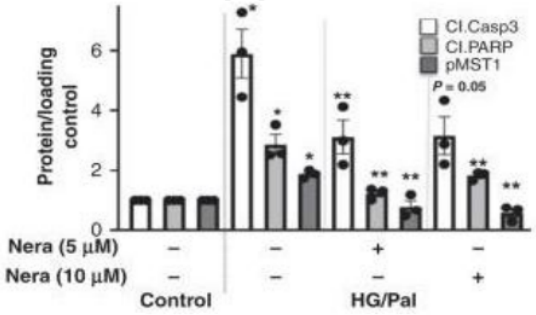
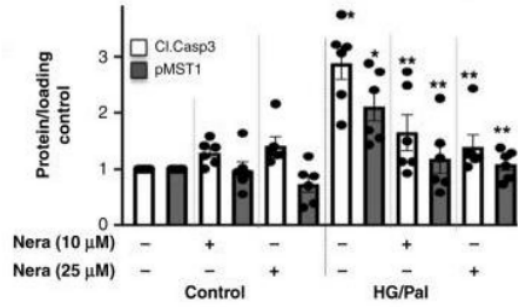
Neratinib as a Novel Treatment for Type 1 Diabetes Mellitus

Ardestani et al., 2019 used the LanthaScreen Eu kinase binding test platform with staurosporine as the positive control in their study. The binding assay revealed that 103-104 nM of Neratinib can block 100% MST activity, with an IC50 of 37.7 nM. Finally, Neratinib was discovered to be a potent inhibitor of MST115 (Attachment 1). To see if neratinib may decrease MST1 activation and death in INS-1E cells under chronic diabetogenic conditions (Graphic 1), researchers exposed the cells to a mixture of 22.2 mM glucose and 0.5 mM palmitate (HG/Pal) for 72 hours and then added neratinib (5 M and 10 M). With Neratinib treatment, the levels of phospho-MST1 (pMST1), Caspase-3, and PARP (Poly (ADP-ribose) polymerase) cleavage, all of which are apoptotic chemicals, decreased significantly. Finally, Neratinib inhibits MST1 and beta-cell death [15].



Graphic 1. Neratinib Blocks MST1 and Apoptosis of Beta Cell [15]

Six independent tests were conducted utilizing human islet preparations from six different organ donors and subjecting them to a mixture of 22.2 mM glucose and 0.5 mM palmitate (HG/Pal) was used to demonstrate the efficacy of Neratinib in human islets (Graphic 2). The experiment employed a higher dose this time, 10 M and 25 M, and there was no harm. MST1 activity and apoptosis in pancreatic islets were potently suppressed by neratinib due to lower caps3 and pMST1. Additional investigation of TUNEL/insulin co-positivity in isolated human islets verified neratinib's anti-apoptotic effect, suggesting that it protects primary human islets from -cell diabetogenic condition-induced apoptosis [15] (Attachment 2).



Graphic 2. Neratinib Blocks Pancreatic Islet of Beta Cell [15]

Neratinib's ability to restore expression of PDX1, a key marker for insulin production and beta-cell glucose metabolism, was investigated in a study (Attachment 3). The islet architecture and diverse insulin-negative cells in MLD–STZ-treated mice were impaired, with lower numbers and expression of PDX1 and neratinib treatment. The results neratinib

back with prior research using MST1-KO mice [20], where PDX1 expression was considerably restored, and β-cell function and survival were highly conserved [15].

Ardestani *et al*., 2019 experimented with mice to test whether neratinib had an effect on glycemia in the T1DM mouse model. Mice were food-deprived overnight, and neratinib was given to the mice after giving it a Streptozotocin (STZ) injection. After that, plasma samples were collected every 5 days for 35 days. By day 3 of post-STZ treatment, hyperglycemia was evident, increasing glucose levels. Neratinib did not influence in nondiabetic control mice. Neratinib-treated mice had lower glucose levels during the study and demonstrated substantially enhanced glucose tolerance [15] (Attachment 4).

Neratinib showed promising efficacy for breast cancer therapy through a 5-year analytical follow-up study of the drug's phase III clinical trial. Neratinib, which was initially concerned about side effects such as diarrhea, nausea, vomiting if given chronically, also did not show evidence of increased risk of those side effects. In addition, no evidence of long-term toxicity effects was identified by comparison with placebo. Therefore, neratinib will also be safe to use for diabetes therapy [23]. The recommendation based on the U.S. Food and Drug Administration (FDA) to lower the incidence and severity of diarrhea that patients may experience is to give anti-diarrheal prophylaxis and the first administration of the drug and continue during the treatment.

Furthermore, monitoring fluids and electrolytes balance also need. Further clinical research to determine the suitability of its tolerability profile in diabetic patients is still needed. Optimization of drug chemistry in Neratinib also needs to be done to increase the effectiveness and selectivity of drugs, limit toxicity, and provide better specificity in diabetes therapy [24].

Oral Delivery Efficacy of Alginate Calcium Coated with Chitosan as a Nanocarrier for Type 1 Diabetes Treatment

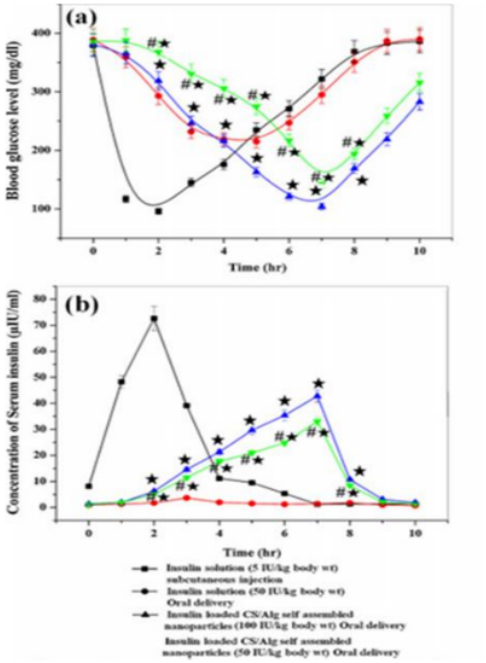
The most effective treatment of type 1 diabetes to control hyperglycemia and other complications for diabetes patients is a subcutaneous injection of insulin. However, this administration method is challenging due to adverse outcomes like possible infection, allergic reaction, needle phobia, and skin bulges. Among the many proposed methods to produce an alternative oral drug for type 1 diabetes, alginate calcium nanocarrier encapsulated with chitosan is a potential ideal oral drug delivery [25].

Alginate is a generic term for natural unbranched polyanionic polysaccharides derived from β-d-mannuronic acid (M) and α-l-guluronic acid found in marine brown algae. It is one of the most commonly used polymers for drug delivery due to its several beneficial traits: biocompatible, non-toxic, non-immunogenic, biodegradable, generally available, mucoadhesive, and low in cost [26]. Alginate can retain and release encapsulated substances in an acidic environment such as the stomach, while it is neutral in alkaline environments such as the small intestine [27]

According to current studies, encapsulating alginate with chitosan, a cationic polysaccharide generated by deacetylation of chitin, promotes medication penetration and absorption in the stomach due to its high mucoadhesive property [17]. Chitosan increases contact duration with intestinal epithelium, improving penetration of epithelial cell tight junctions via paracellular transport. Most notably, after oral consumption, chitosanase enzymes released by bacteria in the colon breakdown chitosan [28].

In diabetic mice, the hypoglycemic effects of oral insulin delivery in alginate calcium microbeads containing chitosan were compared to the control (subcutaneous insulin injection 5 IU/kg/b.w.). After the seventh hour of delivery, blood glucose levels dropped to 143 and 104 mg/dl, respectively, and the impact lasted at least 9 hours. At the seventh hour, maximum

serum insulin levels indicate intestinal epithelial uptake of insulin-loaded nanoparticles and their function to shield insulin from enzymatic destruction in the GI tract [28]. (Graphic 3)



Graphic 3. Orally Administrated Insulin in Alginate Nanocarrier Containing Chitosan Lowered Blood Glucose Significantly and Prolonged Maximum Serum Insulin Concentration in Diabetic Mice In Vivo [28]

The pancreas of diabetic rats treated with metformin hydrochloride encapsulated in chitosan alginate nanoparticles had normal, oval or circular forms with no pathological alterations, according to light microscopic inspection. There was also a decrease in the number of cells with highly eosinophilic cytoplasm and just single cells with vacuolization. Furthermore, the non-toxicity of this developed nanoparticle was demonstrated by no indicators of toxicity or mortality symptoms, as well as no alterations in diabetic rats' behavior or body weight (see attach. 5). [29]

Preparation of Neratinib Loaded Chitosan-Alginate Calcium Nanocarrier for Oral Delivery

Because of its ease of use and lack of toxicity, ionotropic gelation is the most used process for producing alginate-based nanoparticles. In this approach, alginate is ionotropically crosslinked in aqueous solutions by a mechanism known as the "egg-box model," in which adding Ca2+ or other divalent cations chelates alginate and creates a 3D network that allows the loading of biomolecules or pharmaceuticals into the structure.

The neratinib-loaded chitosan-alginate calcium nanocarrier is prepared in two steps. To begin, make a blank chitosan-alginate microbead. Alginate extraction from brown marine algae is accomplished by converting natural alginate in various salt forms by adding aqueous alkali solutions, mainly sodium hydroxide [26]. The initial shell of the nanocarrier is formed

by adding aqueous calcium chloride to the aqueous solution of alginate and then sonicating for 15 minutes with a sonicator [28]. To generate the first shell, calcium cations crosslink with negatively charged alginate via ionotropic gelification. The inclusion of calcium can improve the overall acid resistance of the system, and the outer layer of chitosan can further protect the nanoemulsion. This causes the microbead to have a mucoadhesive action and improves oral absorption. The calcium alginate pre-gel was then sonicated for 25–30 minutes at room temperature with a chitosan solution (Figure. 3) [17, 27].

The ionic interaction between positively charged chitosan and negatively charged alginate coating the microbead results in the formation of a self-assembly microbead with high encapsulation efficiency [28]. The chitosan molecules' excess positive charges can enable more extended attachment with the negatively charged intestinal mucus surface, allowing for sustained release of encapsulated insulin and inhibiting self-aggregation, thereby enhancing its stability [25].

The nanoparticle Neratinib is then loaded into the microbead in the second stage. Neratinib is a quinoline molecule that is also a nitrile. Vortexing Neratinib with preset amounts of pegylated polyamidoamine dendrimers results in Neratinib nanoparticles. Using a nanocarrier can help avoid the side effects of a high Neratinib oral dose [30].

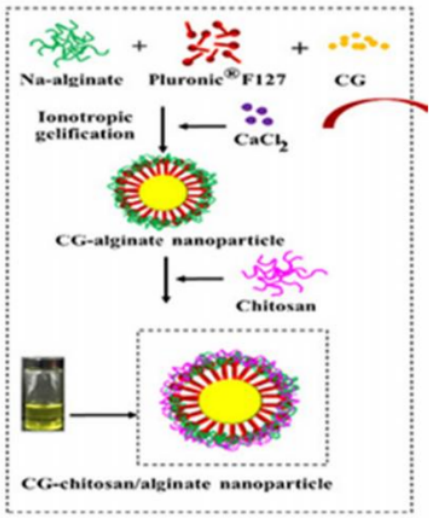


Figure 3 Preparation of Chitosan Alginate Nanoparticle with Ionotropic Gelification

CONCLUSION

Neratinib as a mammalian sterile 20-like kinase 1 (MST1) inhibitor carried by nanocarrier chitosan-alginate is effective for type 1 diabetes mellitus oral drug delivery. This combination can prevent beta-cell apoptosis and dysfunction from restoring beta cells and from preventing severe progress of diabetes. Future perspective needs further experimental and clinical trials to obtain concrete scientific evidence.

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GENERAL COMMENTS

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